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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/738,444	12/15/2000	William E. Jack	NEB-180	9633

28986 7590 10/21/2002

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EXAMINER
LU, FRANK WEI MIN

ART UNIT	PAPER NUMBER
1634	11

DATE MAILED: 10/21/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/738,444	JACK ET AL.	
	Examiner	Art Unit	
	Frank W Lu	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 30-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 30-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12/15/2000 (orginal)* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on July 30, 2002 has been entered as Paper No:10. The claims pending in this application are claims 1-5 and 30-34. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn.

Drawings

2. In the office action on December 9, 2002, the examiner indicated that the drawings was objected to for reasons as stated on FORM PTO-948 (Rev. 8-98) and formal correction of the noted defect can be deferred until the application is allowed by the examiner. However, according to 37 CFR 1.85 (a), the office now is required to submit a proposed drawing correction in reply to this Office action.

Claim Objections

3. Claim 1 is objected to because of the following informality: step (c) should be step(b) since there is no step (b) in the claim.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1 and 3-5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for creating a DNA having the target single-stranded region within a double-stranded region by nicking at least two sites bordering the target region within the double-stranded DNA with at least one site-specific nicking endonuclease, does not reasonably provide enablement for creating a DNA having the target single-stranded region within a double-stranded region by nicking one site bordering the target region within the double-stranded DNA with a site-specific nicking endonuclease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. .

Note that this rejection was made basing on that a DNA having the target single-stranded region within a double-stranded region can not be created after digestion of a double stranded DNA with a site-specific nicking endonuclease and selectively denatured the double stranded DNA if the double stranded DNA only has one site for the site-specific nicking endonuclease.

In *In re Wands*, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court considered the issue of enablement in molecular biology. The Court summarized eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the

breadth of the claims. The Court also stated that although the level of skill in molecular biology is high, results of experiments in molecular biology are unpredictable.

To begin, there is no direction or guidance on how to create a DNA having the target single-stranded region within a double-stranded region by nicking one site bordering the target region within the double-stranded DNA with a site-specific nicking endonuclease. While the relative skill in the art is very high (the Ph.D. degree with laboratory experience), there is no predictability whether a DNA having the target single-stranded region within a double-stranded region can be created by nicking one site bordering the target region within the double-stranded DNA with a site-specific nicking endonuclease if the double stranded DNA only has one site for the site-specific nicking endonuclease.

The invention relates to a method for creating a DNA having the target single-stranded region in a double-stranded DNA. The specification provides working examples (see pages 30 and 31 and Figure 1) to create a DNA having the target single-stranded region within a double-stranded region by nicking at least two sites bordering the target region within the double-stranded DNA with a site-specific nicking endonuclease. Since the specification does not provide a guidance to show how to create a DNA having the target single-stranded region within a double-stranded region by nicking one site bordering the target region within the double-stranded DNA with a site-specific nicking endonuclease, the skilled artisan will have no way to predict the experimental results. In fact, in the examiner's opinion, a DNA having the target single-stranded region within a double-stranded region can only be created after digestion of a double stranded DNA with a site-specific nicking endonuclease and selectively denatured the

double stranded DNA if the double stranded DNA has at least two sites for the site-specific nicking endonuclease. If the double stranded DNA has only one site for the site-specific nicking endonuclease as recited in claim 1, site-specific nicking endonuclease only makes a nick in the double stranded DNA, not a single stranded fragment in double stranded DNA. After selectively denaturation of the target region of double stranded DNA, a single stranded DNA from the target region can not be removed and a DNA having the target single-stranded region within a double-stranded region can not be generated. Accordingly, it is concluded that undue experimentation is required to make the invention as it is claimed.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is rejected as vague and indefinite because dependent claim 2 does not correspond to independent claim 1. Note that claim 1 only needs one nicking site within the double-stranded DNA for site-specific nicking endonuclease while claim 2 needs two nicking sites within the double-stranded DNA for site-specific nicking endonuclease. Please clarify.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 30-34 are rejected under 35 U.S.C. 102(b) as being anticipated by Xu *et al.,* (US Patent No. 5,786,195, published on July 28, 1998).

Regarding claims 30-34, Xu *et al.,* teach a method for cloning and producing the bssHII restriction endonuclease in *E. coli*. *B. stearothermophilus* H3 genomic DNA was digested with a restriction enzyme such as AciI or HinfI. Then the digested DNA samples (less than 10 kb) were self-ligated at a low DNA concentration (less than 2 microgram per ml). The ligated circular DNA was extracted and used as templates for inverse PCR reactions (for example, see column 9). DNA fragments produced by AciI or HinfI was considered as a nucleic acid molecule as recited in claims 30-32 wherein each fragments had three double stranded subfragments (considered digested fragment as three parts) and two single-stranded termini (3' and 5' protruding, cohesive termini produced by AciI or HinfI) since DNA fragments produced by both restriction enzymes had 5' and 3' protruding, cohesive termini (for AciI and HinfI cut sites, see New England Biolabs 96/97 Catalog, pages 13 and 36). The ligated circular DNA was considered as a circular nucleic acid molecule as recited in claim 33 having at least two double stranded subfragments (considered the ligated circular DNA as two or more parts) and two single-stranded termini (3' and 5' protruding, cohesive termini produced by AciI or HinfI). Note that:(1) although Xu *et al.,* did not directly show the double digestion of a pLG339 vector with Xba I and BamHI, this limitation was considered to be inherent to the reference taught by Xu *et*

al., since this vector was used to clone bssHIIR gene amplified in the presence of a forward primer with a Xba I site and a reverse primer with a BamHI site (see column 10). The protruding, cohesive termini in the pLG339 vector produced by Xba I/BamHI digestion before the cloning was considered as two single stranded termini (for sites of Xba I and BamHI, see New England Biolabs 96/97 Catalog, pages 17 and 53); and (2) although the nucleic acid molecules recited in claims 30-34 were not produced by the method of claim 3, it was well established that even though product-by process claims were limited by and defined by the process, the determination of the patentability of the product was based on the product itself. The patentability of a product did not depend on its method of production. If the product in the product-by-process claim was the same as or obvious from a product of the prior art, the claim would be unpatentable even though the prior product was made by a different process."*In re Thorpe*, 227 USPQ 964, 966 (Fed. Cir. 1985).

Therefore, Xu *et al.,* teach all limitations recited in claims 30-34.

10. Claims 1, 33, and 34 are rejected under 35 U.S.C. 102(a) as being anticipated by Wang *et al.,* (Molecular Biotechnology, 15, 97-104, June, 2000).

Wang *et al.,* teach the preparation of DNA substrates for in vitro mismatch repair. As shown in Figure 1, a vector pUC19XE was nicked with N.Bst NBI and then denatured and reannealed with a denatured pUC18HE (see page 100). Note that: (1) a region containing C/G in pUC 19XE was considered as a target region within the double-stranded DNA; (2) reannealed substrate was considered to be a DNA having the target single stranded region (T/G region) in

the double-stranded region; (3) the denaturation step could be considered as step (b) as recited in claim 1; and (4) the nicked vector pUC19XE could be considered to have three or more subfragments with 3' and 5' termini since this vector could be divided into three or more parts.

Although the nucleic acid molecules recited in claims 33 and 34 were not produced by the method of claim 3, it was well established that even though product-by process claims were limited by and defined by the process, the determination of the patentability of the product was based on the product itself. The patentability of a product did not depend on its method of production. If the product in the product-by-process claim was the same as or obvious from a product of the prior art, the claim would be unpatentable even though the prior product was made by a different process."*In re Thorpe*, 227 USPQ 964, 966 (Fed. Cir. 1985).

Therefore, Wang *et al.,* teach all limitations recited in claims 1, 33, and 34.

Response to Arguments

In page 11, first and second paragraph of applicant's remarks, applicant argued that "[T]here is no suggestion or teaching that selective denaturation of target DNA be undertaken so as to create a single stranded region in a double-stranded DNA." in the reference taught by Wang *et al.*.

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection. First, Wang *et al.,* taught to denature pUC19XE plasmid including the target region, the examiner considered that they did selectively denature target region. Second, claim 1 did not limit to denature the target region only.

Conclusion

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. No Claim is allowed.

13. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703) 308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (703) 305-1270. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the Chemical Matrix receptionist whose telephone number is (703) 308-0196.

Frank Lu
October 16, 2002

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600